Rejection of Claim 22 under 35 U.S.C. §101

Claim 22 is rejected under 35 U.S.C. §101 "because the claimed invention is directed to non-statutory subject matter" (Office Action, page 2). The Examiner states that the host cell of Claim 22 is reasonably interpreted to encompass a human being and human beings are non-statutory subject matter. The Examiner suggests inserting the term isolated or cultured prior to the word cell in the claim.

Claim 22 has been amended to recite the term "isolated" thereby obviating the rejection.

Rejection of Claims 1-15 and 20-22 under 35 U.S.C. §112, first paragraph

Claims 1-15 and 20-22 are rejected under 35 U.S.C. §112, first paragraph "because the specification, while being enabling for making a vector comprising a coding sequence encoding a microbial peptide and using said vector in applications, *in vitro*, does not reasonably provide enablement for use of said vector in an animal, *in vivo*" (Office Action, page 3). The Examiner states that the "nature of the invention is gene therapy with anti-microbial peptides" and that the "state of the art using anti-microbial peptides for therapy *in vivo* is not well established" (Office Action, page 4). Citing the Boman (AS), Verma *et al.* and Orkin *et al.* references, the Examiner states that "the art of gene therapy is unpredictable" (Office Action, page 4). The Examiner further states that Applicants' specification "does not teach any dosages of vector that would lead to expression of the encoded peptide at a therapeutic level" and that the working examples in the specification are not "correlatable to use of the claimed vector or methods for therapy *in vivo*" (Office Action, pages 4-5).

Applicants respectfully disagree. The first paragraph of § 112 requires nothing more than objective enablement (*In re Marzocchi & Horton* 169 USPQ 367, 369 (CCPA 1971)). In *Marzocchi* the court stated that:

> a specification disclosure which contains a teaching of the manner and process of making and using the invention in terms which correspond in scope to those used in describing and defining the subject matter sought to be patented *must* be taken as in compliance with the enabling requirement of the first paragraph of § 112 *unless* there is reason to doubt the objective truth of the statements contained therein which must be relied on for enabling support. Assuming that sufficient reason for such doubt does exist, a rejection for failure to teach how to make and/or use will be proper on that basis; such a rejection can be overcome by suitable proofs indicating that the teaching contained in the specification is truly enabling. Id.

The court further stated that

> it is incumbent upon the Patent Office, whenever a rejection on this basis is made, to explain *why* it doubts the truth or accuracy of any statement in a supporting disclosure and to back up assertions of its own with acceptable evidence or reasoning which is inconsistent with the contested statement. Id. at 370.

In the specification as filed, Applicants have shown that administration of a retroviral vector comprising a sequence which codes for antimicrobial peptides, melittin and cecropin, produces anti-tumor effects *in vivo* and anti-viral effects *in vitro*. The court has clearly stated that a rigorous or an invariable exact correlation is not required (*Cross v. Iizuka* 224 USPQ 739, 747 (Fed. Cir. 1985)). Microbial peptides are known to have anti-cancer, anti-HIV and anti-bacterial activities (specification, page 1, line 17 page 4, line 18). Thus, it is not necessary for Applicants to specify the dosage since those of skill in the art can determine dosage without undue experimentation (MPEP, 7th edition, 2164.01(c)page 2100-147). The Examiner cites the Bowman, Verma *et al.* and Orkin *et al.* references as evidence that the state of art using anti-microbial peptides for therapy *in vivo* is not well established, however, these references address clinical applications of gene therapy. Clinical data is not a requirement of patentability (*In re Brana*, 34 USPQ2d 1436, 1441 (Fed. Cir. 1995)). Furthermore,

> the issue of "correlation" is also dependent on the state of the prior art. In other words, if the art is such that a particular model is recognized as correlating to a specific condition, then it should be accepted as correlating unless the examiner has evidence that the model does not correlate. Even with such evidence, the Examiner must weigh the evidence for and against correlation and decide whether one skilled in the art would accept the model as reasonably correlating to the condition (*In re Brana*, 51 F.3d 1560, 1566, 34 USPQ2d 1436, 1441 (Fed. Cir. 1995)) (MPEP, 7th edition, 2164.02, page 2100-148).

The Examiner has not provided evidence to show that one skilled in the art would not accept Applicants' *in vivo* and *in vitro* data as reasonably correlating to the use of the claimed vectors. In fact, the art cited indicates that a person of skill in the art would view Applicants' data as reasonably correlating to the claimed use. For example, Bowman states that "[a]nimal experiments indicate that in some cases cecropin P1 could be useful" (Bowman, page 83). Clearly Applicants have provided an enabling disclosure. Nevertheless, in order to expedite prosecution, the claims have been amended to relate to a recombinant vector for introducing DNA into an eucaryotic cell, the vector comprising, in operable linkage, a) retroviral vector DNA

or at least a portion of the retroviral vector DNA comprising elements necessary for infection and direction of expression in target cells; and b) one or more coding sequences wherein at least one sequence encodes for a naturally occurring therapeutic antimicrobial peptide or a biologically active derivative thereof.

The Examiner further states that "the breadth of the claimed invention is not enabled" (Office Action, page 6). The Examiner notes that the claims recite "antimicrobial peptides or derivatives thereof", and that "Applicants have demonstrated only cecropin A and melittin" and "discuss other amphipathic/lytic peptides such as magainin, defensin, etc" (Office Action, page 6). It is the Examiner's opinion that "Applicants should limit the claims to include only the class of peptides discussed in the specification" (Office Action, page 6).

Applicants respectfully disagree. As noted in the MPEP:

> For a claimed genus, representative examples together with a statement applicable to the genus as a whole will ordinarily be sufficient if one skilled in the art (in view of the level, state of the art and the information in the specification) would expect the claimed genus could be used in that manner without undue experimentation (MPEP, 7th edition, page 2100-148).

In the specification as filed, Applicants have shown that administration of a retroviral vector comprising a sequence which codes for two antimicrobial peptides, melittin and cecropin, produces anti-tumor effects *in vivo* and anti-viral effects *in vitro*. One skilled in the art (in view of the level, state of the art and the information in the specification) would expect the claimed genus could be used as claimed by Applicants without undue experimentation. The Examiner has not provided evidence to show that one skilled in the art would not expect the claimed genus could be used in that manner without undue experimentation. Indeed, Applicants direct the Examiner's attention to the Cooper application, wherein Cooper *et al.* teach the use of lytic peptides for treating infection in a mammal based upon data using the lytic peptide, cecropin.

Thus, Applicants have provided an enabling disclosure for the full scope of the claimed invention.

Rejection of Claims 16-19 and 23-25 under 35 U.S.C. §112, first paragraph

Claims 16-19 and 23-25 are rejected under 35 U.S.C. §112, first paragraph "as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the

invention" (Office Action, pages 6-7). The Examiner states that "[e]ach of the recited claims requires the use of a vector according to the invention for *in vivo* therapy" and that, as discussed above, "the specification does not enable one of skill in the art to use the invention as claimed" (Office Action, page 7).

Applicants respectfully disagree. As discussed above, the Examiner has not provided the requisite evidence showing that one skilled in the art would not accept Applicants' *in vivo* and *in vitro* data as reasonably correlating to the use of the claimed vectors. In fact, Bowman, a person of skill in the art, states that "[a]nimal experiments indicate that in some cases cecropin P1 could be useful" (Bowman, page 83).

Clearly Applicants have provided an enabling disclosure for the full scope of the claimed invention.

Rejection of Claims 1-25 under 35 U.S.C. §112, second paragraph

Claims 1-25 are rejected under 35 U.S.C. §112, second paragraph "as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention" (Office Action, page 7).

The Examiner states that the recitation of "or corresponding to" in relation to DNA of a portion of a retroviral vector and "which is capable of infecting and directing expression" in Claims 1, 9 and 23 is indefinite. The Examiner suggests amending the claims to recite "a portion of retroviral vector DNA comprising elements necessary for infection and direction of expression in target cells" to render the claims more clear.

Claims 1, 9 and 23 have been amended as suggested by the Examiner.

The Examiner states that the recitation of "or derivative thereof" in relation to the antimicrobial peptide in Claims 1, 2, 9, 23 and 25 is indefinite "because it is unclear as to what is encompassed by the claim" (Office Action, page 8).

Applicants respectfully disagree. However, in order to more clearly define the invention, Claims 1, 2, 9, 23 and 25 have been amended to recite "biologically active derivatives thereof". Applicants clearly teach in the specification that:

> The antimicrobial peptides or derivatives thereof include but are not limited to those encoding melittin, the various cecropins and magainins. Further included are the apidaecin and defensin peptides or derivatives thereof. These genes may be expressed in their preproform or alternatively in a genetically engineered

preform or in another form which renders a biological active peptide or a derivative thereof (specification, page 9, lines 5-12).

The Examiner states that the term "antimicrobial peptide" in Claims 1, 2, 9 and 23 "would reasonably be interpreted to mean a peptide which targets a microbe", but "the claims indicate that the peptide is useful against tumor cells and, in claim 23, for correcting a genetic defect" (Office Action, page 8). The Examiner concludes that "it is not clear exactly what peptides are encompassed by the claimed invention" (Office Action, page 8).

Applicants respectfully disagree. An "antimicrobial peptide" is a term of art defined as a peptide made by an animal (including humans), usually with a specificity that is important for the innate immunity (nonadaptive immunity) of that animal (see, for example, Bowman, page 61). Thus, a person of skill in the art is clearly apprized of the scope of the invention.

The Examiner states that the term "treatment" renders Claims 1, 2, 9, 23 and 25 indefinite "because the art provides no definite interpretation and the term is not defined in the specification" (Office Action, page 8).

Applicants respectfully disagree. The term "treatment" is a term of art defined as "the care and management of a patient to combat, ameliorate, or prevent a disease, disorder, or injury" (*Mosby's Medical, Nursing & Allied Health*, 5th edition). Thus, a person of skill in the art is clearly apprized of the scope of the invention. As indicated above, however, the term "treatment" has been deleted from Claims 1, 2 and 9.

The Examiner states that "Claim 2 is indefinite because the claim begins 'the recombinant vector' and later recites 'said coding sequences' without providing any antecedent basis for either recitation" (Office Action, page 9). The Examiner suggests amending the claim to provide antecedent basis.

Claim 2 has been amended to depend from Claims 1, thereby providing antecedent basis.

The Examiner states that Claim 11 recites "a retroviral particle produce by" indicating the claim should depend upon a method or process claim in which following the steps of the claim would lead to the particle claimed.

Claim 11 has been amended to more clearly recite a retroviral particle produced by the recombinant retroviral vector system according to Claim 9 after transfecting the packaging cell line with the retroviral vector.

The Examiner states that "Claims 17 and 18 provide for the use of the vector of claim 1, or the vector system of claim 9, respectively, but, since the claim does not forth any steps

involved in the method/process, it is unclear what method/process applicant is intending to encompass" (Office Action, page 9). Claims 17 and 18 are also rejected under 35 U.S.C. §101 "because the claimed recitation of a use, without setting forth any steps involved in the process, results in an improper definition of a process, i.e., results in a claim which is not a proper process claim under 35 U.S.C. 101" (Office Action, page 9).

Claims 17 and 18 have been amended to recite proper method claims.

The Examiner states that Claim 22 "is indefinite because the claim is directed to a host cell without reciting that the cell is isolated or cultured" (Office Action, page 10).

Claim 22 has been amended to indicate that the host cell is isolated.

Rejection of Claims 1-15, 17-19 and 20-22 are rejected under 35 U.S.C. §103(a)

Claims 1-15, 17-19 and 20-22 are rejected under 35 U.S.C. §103(a) "as being unpatentable over Cooper et al., WO 95/01095 in view of Gunzberg et al., WO 96/07748" (Office Action, page 10). The Examiner states that Cooper *et al.* "teach transposon-based vectors comprising sequences encoding lytic peptides" which include melittins, magainins, defensin and cecropins (Office Action, page 10). The Examiner further states that Cooper *et al.* "teach that genes coding for lytic peptides can be transferred and stably expressed in mammalian, vertebrate, and animal cells", but "do not teach the use of a retroviral vector or a vector comprising DNA of a portion of a retroviral vector" (Office Action, pages 10-11). The Examiner states that Gunzberg *et al.* "teach promoter conversion retroviral vectors", but, "do not teach that the coding sequences encode antimicrobial peptides" (Office Action, page 11). It is the Examiner's opinion that:

> [r]etroviruses are well known and widely used in the art as a vector for transferring genes into eukaryotic cells. The skill level in the art of molecular biology is very high. Gunzberg et al. teach that the vectors disclosed in '748 have superior qualities thereby motivating one of skill in the art to substitute the retroviral vectors in place of the transposon based vectors to transfer, express and produce lytic peptides in eukaryotic cells Therefore, it would have been *prima facie* obvious at the time the invention was made to make and use a retroviral vector, which is U3- in the 3' LTR in which a polylinker is inserter [sic] in its place, comprising coding sequences encoding lytic peptides (Office Action, pages 11-12).

The Examiner notes that the instant rejection may be overcome by perfecting the priority claim.

As discussed above, Applicants have perfected the priority claim by filing concurrently herewith certified copies of PCT/EP96/01001 and DK 0243/95. Thus, the rejection has been obviated.

Rejection of Claims 1-15, 17-19 and 20-22 under 35 U.S.C. §103(a)

Claims 1-15, 17-19 and 20-22 are rejected under 35 U.S.C. §103(a) "as being unpatentable over Cooper et al. in view of Temin et al., US 5,124,263 or Gilboa US 5,685,775" (Office Action, page 12). The Examiner refers to the discussion of Cooper *et al.* above. The Examiner states that Temin *et al.* "teach a system for growing stocks of replication incompetent retroviruses" which "has much less risk of recombination events in helper (packaging) cell" (Office Action, page 12). The Examiner states that Temin *et al.* also teach helper cells for production of the retroviral particles and that this system is superior because it reduces risk of recombination and producing replication competent virus, and makes the vectors useful in a broader host range. The Examiner notes that Temin *et al.* "do not suggest inserting coding sequences which code for antimicrobial peptides, nor do they teach that any other heterologous sequences would be inserted into the U3 region" (Office Action, page 12). The Examiner states that Gilboa teaches double copy retroviral vectors wherein a gene is inserted into the 3' U3 region such that when transcribed, the gene also appears in the 5' U3 region; a second gene can be inserted between the LTRs; portions of the U3 region may also be deleted; the gene inserted into the U3 region may also have an internal promoter; packaging cells and production of virion particles; and infection of cells with the virion produced from the packaging cells. The Examiner states that Gilboa does not teach that the non-selectable gene inserted between the LTRs would be a coding sequence encoding antimicrobial peptides or that a polylinker comprising a unique restriction site was inserted into the U3 region. The Examiner further states, however, that "it is likely that this was done as polylinkers comprising unique restriction sites are routinely inserted into vectors to allow ease in cloning" (Office Action, page 13). The Examiner concludes that:

> [r]etroviruses are well known and are widely used to transfer genes into eukaryotic cells. The level of skill in the art of molecular biology is very high. Both Gilboa and Temin et al. suggest that the disclosed vectors are superior vectors for transferring genes to eukaryotic cells. One of skill in the art would be motivated to use the retroviral vectors as disclosed by Temin et al. or Gilboa to transfer lytic peptides to eukaryotic cells as demonstrated by Cooper et al., but using another vector system. Therefore, it would have been prima facie obvious at the time the invention was made

> to substitute retroviral vectors as taught by Temin et al. or Gilboa in place of the transposon based vectors used by Cooper et al. to transfer coding sequences encoding lytic peptides to eukaryotic cells (Office Action, pages 13-14).

Applicants respectfully disagree. Cooper *et al.* developed a transposon-based construct which includes the gene for the native cecropin peptide and the native cecropin promoter and which was inducibly expressed in mammalian and fish cells (Cooper *et al.*, page 13, lines 9-12). As noted by the Examiner, Cooper *et al.* do not suggest the use of retroviral vectors to express the cecropin peptide.

Temin *et al.* teach an improved helper cell for growing up stocks of replication incompetent retrovirus vectors which resists recombination events due to the fact that natural promoters and poly(A) sequences in the helper sequences have been replaced with foreign promoters and poly(A) sequences bearing little or no homology. Temin *et al.* demonstrate the use of the helper cell with the JD220SVHy vector which has a U3 deletion in the right hand LTR region thereby reducing the risk of propagation of the retrovirus. However, Temin *et al.* do not suggest replacing the deleted U3 region with a heterologous sequence.

Gilboa teaches a double copy vector in which a gene is placed within the U3 region of the 3' LTR of the provirus wherein the gene is transferred to the 5' LTR and the 3' LTR of the progeny provirus thereby generating two copies of the transduced gene. Gilboa does not teach the use of antimicrobial peptides in the double copy vectors.

An obviousness rejection requires both (1) that "the prior art would have suggested to the person of ordinary skill in the art that they should . . . carry out the claimed process"; and (2) that the prior art should establish a reasonable expectation of success. In re Vaeck, 20 U.S.P.Q.2d 1438, 1442 (Fed. Cir. 1991). "Both the suggestion and the reasonable expectation of success must be founded in the prior art, not in applicant's disclosure." Id. In discussing obviousness, the court has further stated that

> [a]n invention is not obvious merely because it is a combination of old elements each of which was well known in the art at the time the invention was made. . . Rather, if such a combination is novel, the issue is whether bringing them together as taught by the patentee was obvious in light of the prior art. . . The critical inquiry is whether 'there is something in the prior art as a whole to *suggest* the desirability, and thus obviousness of making the invention' (*Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*13 USPQ2d 1737 at 1765).

That is, the issue is "whether the teachings of the prior art would, *in and of themselves and without the benefit of appellant's disclosure,* make the invention as a whole, obvious" (*In re Sponnoble* 160 USPQ237 at 243 (CCPA 1969)). Clearly the art cited does not suggest using a retroviral vector to express antimicrobial peptides. The prior art combination of record has been made with the impermissible advantage of hindsight, and thus, the rejection is legally improper. That is, in making the obviousness rejection, the Examiner has read the prior art with the benefit of Applicant's disclosure in which there is a clear teaching of the desirability of using a retroviral vector to express an antimicrobial peptide. As the court made clear in *In re Dow*, it is not legally correct to rely on Applicant's disclosure for the suggestion that the cited references should be combined and the expectation of success. In the present case, the suggestion or motivation for combining the references and the expectation of success are not found in the prior art, but rather in Applicant's disclosure.

Even if the rejection were proper, the combination of cited art would not render obvious Applicants' claimed invention. Applicants teach the use of a retroviral vector to express antimicrobial peptides. After transfection of the vector into a cell (*e.g.,* the human bladder carcinoma cell line described in the exemplification), the retroviral vector is integrated into the genomic DNA of the cell line. Subsequently, the transcription and translation machinery of the host cell is used to produce the antimicrobial peptide, however, initiation of transcription of the peptide gene is driven by the retroviral vector. As indicated in the subject application, at the time of Applicants' invention it was known that antimicrobial peptides have anti-retroviral activities (*e.g.,* specification, page 1, lines 21-22 and Wachinger, M., *et al., FEBS, 309(3):*235-241 (1992) cited as reference AX on PTO form 1449 mailed to the Patent Office on September 10, 1998). Wachinger *et al.* (AX) clearly teach that melittin interferes with the processing of the gag/pol protein precursors of HIV (Wachinger *et al.* (AX), page 240, column 2). These findings have been confirmed in the subsequent publication, Wachinger, M., *et al., J. Gen. Virol., 79*:731-740 (1998), a copy of which is being filed as the Exhibit. Clearly at the time of Applicants' invention, a person of skill in the art would not be motivated to insert an antimicrobial gene into a retroviral vector for expression purposes because the skilled person would not expect to obtain adequate expression of the antimicrobial peptide from a retroviral vector. Based on the knowledge at the time of Applicants' invention, a person of skill in the art would expect that the initial expression of the antimicrobial peptide would inhibit further transcription and mRNA synthesis of the antimicrobial peptide and would thus, down regulate further antimicrobial

peptide synthesis. Thus, Applicants' teaching that a retroviral vector can be used to express antimicrobial peptides is a surprising and unexpected result.

The combined teaching of Cooper et al. in view of Temin et al., US 5,124,263 or Gilboa US 5,685,775 does not render obvious Applicants' claimed invention.

CONCLUSION

In view of the above amendments and remarks, it is believed that all claims are in condition for allowance, and it is respectfully requested that the application be passed to issue. If the Examiner feels that a telephone conference would expedite prosecution of this case, the Examiner is invited to call the undersigned at (781) 861-6240.

Respectfully submitted,

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